(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 138 441**
B1

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **03.08.88**

(21) Application number: **84306512.9**

(22) Date of filing: **25.09.84**

(51) Int. Cl.[4]: **C 07 C 143/00,** C 07 D 309/06, C 07 H 9/04, A 61 K 31/095, A 61 K 31/35, A 61 K 31/70

(54) **Anticonvulsant sulfamate derivatives.**

(30) Priority: **26.09.83 US 535475**

(43) Date of publication of application:
24.04.85 Bulletin 85/17

(45) Publication of the grant of the patent:
03.08.88 Bulletin 88/31

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI NL SE

(56) References cited:

THE JOURNAL OF ORGANIC CHEMISTRY, vol. 42, no. 19, 16th September 1977, pages 3173-3180; G.H. POSNER et al.: "Organic reactions at alumina surfaces. A mechanistic and synthetic study of sulfonate ester elimination reactions effected by chromatographic alumina"

JOURNAL OF MEDICINAL CHEMISTRY, vol. 24, no. 7, July 1981, pages 901-903, American Chemical Society, US; A.F. HIRSCH et al.: "Synthesis and evaluation of the male antifertility properties of a series of N-unsubstituted sulfamates"

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(56) References cited:

CHEMICAL ABSTRACTS, vol. 81, no. 11, 16th September 1974, page 502, no. 63892k, Columbus, Ohio, US; N.K. KOCHETKOV et al.: "Monosaccharides. XXIX. New variant of the synthesis of amidosulfates using ethoxyacetylene"

Courier Press, Leamington Spa, England.

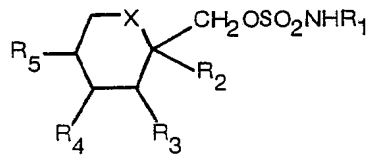
EP 0 138 441 B1

Description

Sulfamates of various structures, including those derived from monosaccharides are described in references such as N. K. Kochetkov et al in Zhurnal Obshchei Kimii, Vol. 41, No. 8, 1866 to 1871 (1971), Vol. 42, No. 12, 2755 to 2757 (1972) and Vol. 44, No. 4, 871 to 875 (1974) and in Doklady Akademii Nauk SSR, Vol. 216, No. 1, 97 to 100 (1974); T. Tscuhiya et al., in Tetrahedron Letters, No. 36, 3365 to 3368 (1978); and A. F. Hirsch in Journal of Medicinal Chemistry, 24, 901 to 903 (1981) and U.S. Patent 4,075,351.

Summary of the Invention

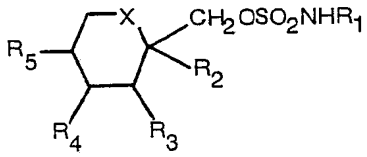
It has been found that sulfamates of the following formula (I):



(I)

wherein X is O or CH_2 and R_1, R_2, R_3, R_4 and R_5 are as hereinafter defined, possess anticonvulsant activity in mammals and are thus useful in treating disease states such as epilepsy and glaucoma. Also part of the present invention are pharmaceutical compositions containing one or more sulfamates of formula (I). Methods for the treatment e.g., prevention, of convulsions using such compositions are also described.

The sulfamates of the invention are of the following formula (I):



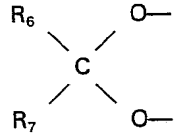
(I)

wherein

X is CH_2 or oxygen;

R_1 is hydrogen or alkyl (e.g. C_1 to C_6 alkyl) and

R_2, R_3, R_4 and R_5 are independently hydrogen or lower alkyl (e.g. C_1 to C_4 alkyl), and, when X is CH_2, R_4 and R_5 may be joined to form a benzene ring and, when X is oxygen, R_2 and R_3 and/or R_4 and R_5 together may be a methylenedioxy group of the following formula (II):



(II)

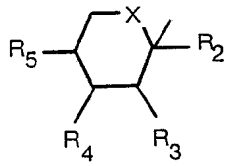
wherein R_6 and R_7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

R_1 is preferably hydrogen or alkyl of 1 to 4 carbons, such as methyl, ethyl and iso-propyl. Alkyl throughout this specification includes straight and branched chain alkyl. Specific alkyl group for R_2, R_3, R_4, R_5, R_6 and R_7 include methyl, ethyl, iso-propyl and n-propyl. When X is CH_2, R_4 and R_5 may combine to form a benzene ring fused to the 6-membered X-containing ring, i.e., R_4 and R_5 are defined by the alkatrienyl group = CH—CH = CH—CH =.

A particular group of compounds of formula (I) is that wherein X is oxygen and both R_2 and R_3 and R_4 and R_5 together are methylenedioxy groups of the formula (II) wherein R_6 and R_7 are both hydrogen, both alkyl or combine to form a spiro cyclopentyl or cyclohexyl ring, in particular where R_6 and R_7 are both alkyl such as methyl. A second group of compounds is that wherein X is CH_2 and R_4 and R_5 are joined to form a benzene ring. A third group of compounds of formula (I) is that wherein both R_2 and R_3 are hydrogen.

The compounds of formula (I) may be synthesized by the following methods:

a) Reaction of an alcohol of the formula RCH_2OH with a chlorosulfamate of the formula $ClSO_2NH_2$ or $ClSO_2NHR_1$ in the presence of a base such as potassium t-butoxide or sodium hydride at a temperature of about −20 to 25°C and in a solvent such as toluene, THF or dimethylformamide wherein R is a moiety of the following formula (III):



(III)

b) Reaction of an alcohol of the formula RCH_2OH with sulfurylchloride of the formula SO_2Cl_2 in the presence of a base such as triethylamine or pyridine at a temperature of about −40 to 25°C in a solvent such as diethyl ether or methylene chloride to produce a chlorosulfate of the formula RCH_2OSO_2Cl.

The chlorosulfate of the formula RCH_2OSO_2Cl may then be reacted with an amine of the formula R_1NH_2 at a temperature of about −40 to 25°C in a solvent such as methylene chloride or acetonitrile to produce a compound of formula (I). The reaction conditions for b) are also described by T. Tsuchiya et al in Tet. Letters, No. 36, p. 3365 to 3368 (1978).

c) Reaction of the chlorosulfate RCH_2OSO_2Cl with a metal azide such as sodium azide in a solvent such as methylene chloride or acetonitrile yields an azidosulfate of the formula $RCH_2OSO_2N_3$ as described by M. Hedayatullah in Tet. Lett. P. 2455—2458 (1975). The azidosulfate is then reduced to a compound of formula (I) wherein R_1 is hydrogen by catalytic hydrogenation, e.g. with a noble metal and H_2 or by heating with copper metal in a solvent such as methanol.

The starting materials of the formula RCH_2OH may be obtained commercially or as known in the art. For example, starting materials of the formula RCH_2OH wherein both R_2 and R_3 and R_4 and R_5 are identical and are of the formula (II) may be obtained by the method of R. F. Brady in Carbohydrate Research, Vol. 15, p.35 to 40 (970) or by reaction of the trimethylsilyl enol ether of a R_6COR_7 ketone or aldehyde with fructose at a temperature of about 25°C in a solvent such as halocarbon, e.g. methylene chloride in the presence of a protic acid such as hydrochloric acid or a Lewis such as zinc chloride. The trimethylsilyl enol ether reaction is described by G. L. Larson et al in J. Org. Chem. Vol. 38, No. 22, p. 3935 (1973).

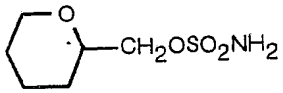
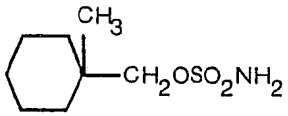
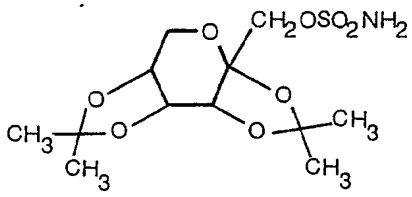
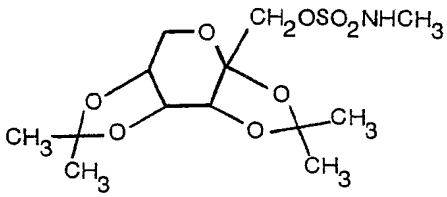
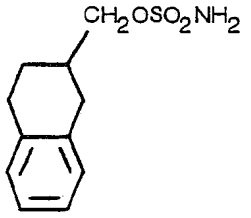
Further, carboxylic acids and aldehydes of the formulae RCOOH and RCHO may be reduced to compounds of the formula RCH_2OH by standard reduction techniqeus, e.g. reaction with lithium aluminum hydride, sodium borohydride or borane-THF complex in an inert solvent such as diglyne, THF or toluene at a temperature of about 0 to 100°C, e.g., as described by H. O. House in "Modern Synthetic Reactions", 2nd Ed., pages 45 to 144 (1972).

The compounds of the invention include the various individual isomers as well as the racemates thereof, e.g., the various alpha and beta atachments, i.e., below and above the plane of the drawing, of R_2, R_3, R_4 and R_5 on the 6-membered ring. Preferably, the oxygens of the methylenedioxy group (II) are attached on the same side of the 6-membered ring.

The compounds of formula (I) are useful as anticonvulsant agents. The anticonvulsant activity of the subject compounds was determined using a standard "maximal electroshock test" (MES). In this test, activity is indicated by a block of the tonic extensor seizure caused by application of an electric shock to mice via corneal electrodes, as described by Swinyard et al in J. Pharmacol. Exptl, Therap. 106, 319 (1952), and recorded as % block. A more recent description of current anticonvulsant drug screening is given in Swinyard et al in Epilepsia 19, 409 (1978).

The anticonvulsant activity of compounds of this invention tested according to the Swinyard (1952) method is shown in the following Table I:

TABLE I

Example	Compound	MES test ED_{50} *(mg/kg, i.p.)
1		195
2		270
3		26
4		70% block at 200 mg/kg, i.p.
5		55

* Unless otherwise noted.

For treating epilepsy, a compound of formula (I) may be employed at a daily dosage in the range of about 30 to 2000 mg, usually in 2 to 4 divided doses, for an average adult human. A unit dose would contain about 10 to 500 mg of the active ingredient.

In general, compounds of formula (I) may be used in treating epilepsy in a manner similar to that used for phenytoin. Medical aspects of the treatment of epilepsy are described by L. S. Goodman et al in "The Pharmacological Basis of Therapeutics", 5th Ed. pages 201 to 226, Macmillan (1975).

Further, compounds of formula (I) are inhibitors of carbonic anhydrase, as determined by the methods described by S. J. Dodgson et al in the Proc. Natl. Acad. Sci., U.S.A., 77, pages 5562 to 5566 (1988) or by N. Itada et al in the Journal Biol. Chem., 252, pages 3881 to 3890 (1977) and as such, are useful in the treatment of glaucoma. The relationship between the treatment of glaucoma and carbonic anhydrase inhibition is described by A. Stein et al in the American Journal of Opthalmology, 95:222—228 (1983). For the treatment of glaucoma, a compound of formula (I) may be administered systemically, e.g. by oral or parenteral routes as described below, or topically in the eye in a mineral oil solution or suspension, or aqueous suspension. When used systemically, the compound would be administered in an amount of about 50 to 500 mg per day for an average adult human, while the topical dosage would be about 1 to 3 drops (per eye) of a solution or suspension containing about 1 to 5% by weight of a compound of formula (I) with the dosage being administered about 1 to 4 times per day.

To prepare the parmaceutical composition of this invention, one or more sulfamate compounds of formula (I) are intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral, by suppository, or parenteral. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for

liquid oral preparations, such as, for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. Suppositories may be prepared, in which case cocoa butter could be used as the carrier. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility of for preservation, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful, suppository and the like, from about 10 to about 500 mg of the active ingredient.

The foregoing compositions are particularly suitable for use in the treatment of epilepsy or the symptoms of epilepsy by a method comprising internally administering to a subject suffering from the symptoms of epilepsy compositions comprising an effective epilepsy inhibiting amount of a compound of formula (I).

Also part of the present invention are intermediates of the formulae RCH_2OSO_2Cl and $RCH_2OSO_2N_3$.

In the following Examples and throughout the specification the following abbreviations may be used: g (grams); ml (milliliters); min (minutes); hr (hours); mol (moles); cm (centimeters); v/v (volumes to volume); mp (melting point); TLC (thin layer chromatography); NMR (nuclear magnetic resonance); IR (infrared); DMF (dimethylformamide); THF (tetrahydrofuran); and C, H. N. etc. (the chemical symbols for the elements).

Example 1

(Tetrahydro-2H-pyran-2-yl)methane sulfamate

To a cold solution (−5°C) of tetrahydropyran-2-methanol (2.33 g, 0.02 mol) in DMF (40 ml) was added 50% oily sodium hydride (1.17 g, 0.024 mol as NaH). After stirring for 45 min, sulfamoyl chloride (3.42 g, 0.03 mol) was added and the stirring continued for an additional 45 min, at −5°C. The reaction mixture was poured into cold water and extracted with chloroform. The organic layer was dried (Na_2SO_4) and the solvents were removed under vacuum to give a syrup which was dry column chromatographed (eluted with ethyl acetate:hexane, 4:1 v/v) to give pure (tetrahydro-2H-pyran-2-yl) methanesulfamate as a pale yellow syrup, IR:($CHCl_3$) 1180 cm^{-1} and 1370 cm^{-1} (OSO_2NH_2).

Example 2

(1-Methylcyclohexyl)methane sulfamate

To a cold solution (−4°C) of (1-methylcyclohexyl)methanol (6.2 g, 0.048 mol) in DMF (90 ml) was added 50% oily sodium hydride (2.81 g, 0.059 mol as NaH). After stirring for 1 hr, sulfamoyl chloride (7.82 g, 0.062 mol) was added and the stirring was continued for an additional 30 min at −4°C. The reaction mixture was poured into cold water and extracted with toluene. The organic layer was dried (Na_2SO_4) and the solvents were removed under vacuum to give a syrup which crystallized upon cooling. Recrystallization from chloroform/hexane gave pure (1-methylcyclohexyl)methane sulfamate, mp 40°—42°C.

Example 3

2,3:4,5-Bis-O-(1-methylethylidene)-ß-D-fructopyranose sulfamate

To a cold solution (−4°C) of 2,3:4,5-di-O-isopropylidene-ß-fructopyranose (75 g, 0.29 mol) in DMF (725 ml) was added 50% oily sodium hydride (16.34 g, 0.34 mol as NaH). After stirring for 90 min, sulfamoyl chloride (54.9 g, 0.49 mol) was added and the stirring continued for an aditional 3.5 hr at that temperature. The reaction mixture was poured into cold water and extracted with toluene. The organic layer was dried (Na_2SO_4) and the solvents removed under vacuum to give a syrup which crystallized immediately. Recrystallization from ethylacetate/hexane gave pure 2,3:4,5-bis-O-(1-methylethylidene)-ß-D-fructopyranose sulfamate, mp 125°—126°C.

Example 4

2,3:4,5-Bis-O-(1-methylethylidene)-ß-D-fructopyranose methyl sulfamate

A solution of sulfonyl chloride (93 ml, 1.15 mol) in methylene chloride (100 ml) was added dropwise to a cold solution (−35°C) of 2,3:4,5-di-O-isopropylidene-ß-D-fructopyranose (150 g, 0.58 mol) in methylene chloride (400 ml) and pyridine (150 ml). The reaction mixture was allowed to stir and warm to room temperature (25°C); it was stirred for an additional 2 hr. Solvents were removed under vacuum. The resulting semi-solid was dissolved in anhydrous acetonitrile (35 g, 150 ml) and methyl amine was bubbled in. The reaction mixture was tightly stoppered and solvents removed under vacuum. The resulting syrup was subjected to liquid chromatography (dry column ethyl acetate: hexane, 4:1) yielding a light yellow syrup, 2,3:4,5-bis-O-(1-methylethylidene)-ß-D-fructopyranose methylsulfamate, which was homogeneous by TLC at ^1H NMR.

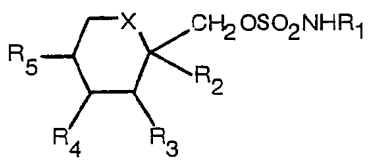
Example 5

(1,2,3,4-Tetrahydro-2-naphthalenyl)methyl sulfamic acid ester

To a cold solution (−5°) of (1,2,3,4-tetrahydro-2-naphthalenyl)methanol (7.1 g, 0.044 mol) in DMF (80 ml) was added 50% oily sodium hydride (2.56 g, 0.054 mol as NaH). After stirring for 45 min, sulfamoyl chloride (6.6 g, 0.057 mol) was added and the stirring continued for an additional 95 min at −5°C. The rection mixture was poured into cold water and extracted with toluene. The organic layer was dried (Na_2SO_4) and the solvents removed under vacuum to give a syrup which crystallized immediately. Recrystallization from chloroform/hexane gave pure (1,2,3,4-tetrahydro-2-naphthalenyl)methyl sulfamic acid ester, mp 108—109°C, as a white solid.

Claims

1. A sulfamate of the following formula (I):



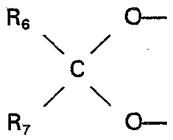
(I)

wherein

X is CH_2 or oxygen;

R_1 is hydrogen or alkyl; and

R_2, R_3, R_4 and R_5 are independently hydrogen or lower alkyl and, when X is CH_2, R_4 and R_5 may be joined to form a benzene ring and, when X is oxygen, R_2 and R_3 and/or R_4 and R_5 together may be a methylenedioxy group of the following formula (II):



(II)

wherein

R_6 and R_7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

2. The sulfamate of Claim 1, wherein X is oxygen; and R_2 and R_3 and R_4 and R_5 together are methylenedioxy groups of the formula (II).

3. The sulfamate of Claim 1, wherein X is CH_2; and R_4 and R_5 are joined to form a benzene ring.

4. The sulfamate of Claim 3, wherein R_2 and R_3 are hydrogen.

5. The sulfamate of Claim 1, wherein said alkyl group for R_1 is alkyl of 1 to 4 carbons; said lower alkyl group for R_2, R_3, R_4 and R_5 is alkyl of 1 to 3 carbons; and said lower alkyl for R_6 and R_7 is alkyl of 1 to 3 carbons.

6. The sulfamate of Claim 1, wherein said sulfamate of formula (I) is selected from the group consisting of:

(tetrahydro-2H-pyran-2-yl) methane sulfamate;

(1-methylcyclohexyl)methane sulfamate;

2,3:4,5-bis-O-(1-methylethylidene)-ß-D-fructopyranose sulfamate;

2,3:4,5-bis-O-(1-methylethylidene)-ß-D-fructopyranose methylsulfamate; or

(1,2,3,4-tetrahydro-2-naphthalenyl)methyl sulfamic acid ester.

7. The sulfamate of Claim 6, wherein said sulfamate is 2,3:4,5-bis-O-(1-methylethylidene)-ß-D-fructopyranose sulfamate.

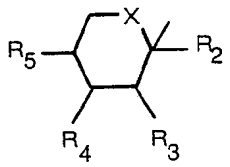
8. The sulfamate of Claim 6, wherein said sulfamate is (1,2,3,4-tetrahydro-2-naphthalenyl)methyl sulfamic acid ester.

9. A pharmaceutical composition comprising a sulfamate of any preceding claim and a pharmaceutically acceptable carrier.

10. The pharmaceutical composition of Claim 9, wherein said sulfamate is present in a unit dosage amount of 10 to 500 milligrams of the sulfamate.

11. A sulfamate according to any of Claims 1 to 8, or a pharmaceutical composition according to Claim 9 or Claim 10, for use in the treatment of convulsions in a mammal.

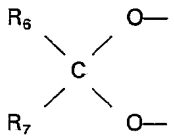
12. A chlorosulfate of the formula RCH_2OSO_2Cl or an azidosulfate of the formula $RCH_2OSO_2N_3$ wherein R is of the following formula (III):



(III)

wherein

R_2, R_3, R_4 and R_5 are independently hydrogen or lower alkyl and, when X is CH_2, R_4 and R_5 may be alkene groups joined to form a benzene ring and, when X is oxygen, R_2 and R_3 and/or R_4 and R_5 together may be a methylenedioxy group of the following formula (II):



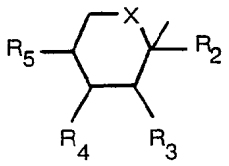
(II)

wherein

R_6 and R_7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

13. A method of making a sulfamate according to claim 1, comprising

(a) reacting an alcohol of the formula RCH_2OH with a chlorosulfamate of the formula $ClSO_2NHR_1$ in the presence of a base, wherein R is a moiety of the formula (III):



(III)

and wherein X, R_1, R_2, R_3, R_4 and R_5 are as defined in claim 1, or

(b) reacting an alcohol of the formula RCH_2OH with sulfurylchloride in the presence of a base, to produce a chlorosulfate of the formula RCH_2OSO_2Cl, wherein R is as defined above, and

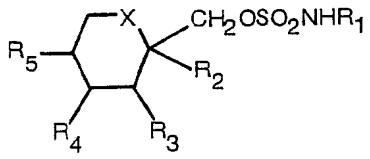
(i) when R_1, in formula (I) is hydrogen or alkyl, reacting said chlorosulfate with an amine of formula R_1NH_2 or

(ii) when R_1 in formula (I) is hydrogen, reacting said chlorosulfate with a metal azide of formula $RCH_2OSO_2N_3$ and reducing said azidosulfate.

14. A method of making a pharmaceutical composition comprising mixing a sulfamate according to claim 1 with a pharmaceutically-acceptable carrier.

Patentansprüche

1. Sulfamat mit der nachstehenden Formel (I):



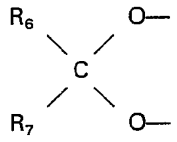
(I)

worin

X für CH_2 oder Sauerstoff steht;

R_1 Wasserstoff oder Alkyl bedeutet; und

R_2, R_3, R_4 und R_5 unabhängig voneinander Wasserstoff oder Niederalkyl bedeuten und, falls X für CH_2 steht, R_4 und R_5 unter Ausbildung eines Benzolringes verbunden sein können und, falls X Sauerstoff bedeutet, R_2 und R_3 und/oder R_4 und R_5 gemeinsam eine Methylendioxygruppe der nachfolgenden Formel (II):



(II)

darstellen können, in welcher Formel

R_6 und R_7 gleich oder verschieden sind und Wasserstoff oder Niederalkyl bedeuten oder Alkyl darstellen und zu einem Cyclopentyl- oder Cyclohexylring verbunden sind.

2. Sulfamat nach Anspruch 1, worin

X für Sauerstoff steht; und

R_2 und R_3 und R_4 und R_5 zusammen Methylendioxygruppen der Formel (II) bedeuten.

3. Sulfmat nach Anspruch 1, worin

X für CH_2 steht; und

R_4 und R_5 unter Ausbildung eines Benzolringen verbunden sind.

4. Sulfamat nach Anspruch 3, worin

R_2 und R_3 Wasserstoff bedeuten.

5. Sulfamat nach Anspruch 1, worin die Alkylgruppe für R_1 Alkyl mit 1 bis 4 Kohlenstoffatomen bedeutet; die Niederalkylgruppe für R_2, R_3, R_4 und R_5 Alkyl mit 1 bis 3 Kohlenstoffatomen bedeutet; und das Niederalkyl für R_6 und R_7 Alkyl mit 1 bis 3 Kohlenstoffatomen bedeutet.

6. Sulfamat nach Anspruch 1, worin das Sulfamat der Formel (I) aus der aus:

(Tetrahydro-2H-pyran-2-yl)methansulfamat;

(1-Methylcyclohexyl)methansulfamat;

2,3:4,5-Bis-O-(1-methylethyliden)-ß-D-fructopyranosesulfamat;

2,3:4,5-Bis-O-(1-methylethyliden)-ß-D-fructopyranosemethylsulfamat; oder

(1,2,3,4-Tetrahydro-2-naphthalinyl)methylsulfaminsäureester bestehenden Gruppe ausgewählt ist.

7. Sulfamat nach Anspruch 6, worin das Sulfamat 2,3:4,5-Bis-O-(1-methylethyliden)-ß-D-fructopyranosesulfamat ist.

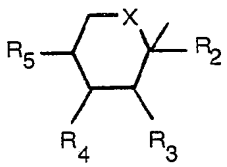
8. Sulfamat nach Anspruch 6, worin das Sulfamat (1,2,3,4-Tetrahydro-2-naphthalinyl)methylsulfaminsäureester ist.

9. Pharmazeutische Zusammensetzung, enthaltend ein Sulfamat nach einem vorstehenden Anspruch und einen pharmazeutisch annehmbaren Trägar.

10. Pharmazeutische Zusammensetzung nach Anspruch 9, worin das Sulfamat in einer Einheitsdosismenge von 10 bis 300 mg Sulfamat vorliegt.

11. Sulfamat nach einem der Ansprüche 1 bis 8, oder pharmazeutische Zusammensetzung nach Anspruch 9 oder 10, zur Anwendung in der Behandlung von Krämpfen bei einem Säuger.

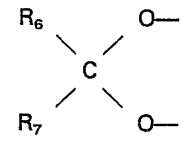
12. Chlorsulfat mit der Formel RCH_2OSO_2Cl oder Azidosulfat der Formel $RCH_2OSO_2N_3$, worin R der folgenden Formel (III):



(III)

entspricht, worin

R_2, R_3, R_4 und R_5 unabhängig voneinander Wasserstoff oder Niederalkyl bedeuten und, wenn X für CH_2 steht, R_4 und R_5 unter Ausbildung eines Benzolringes verbundene Alkengruppen sein können und, wenn X für Sauerstoff steht, R_2 und R_3 und/oder R_4 und R_5 zusammen eine Methylendioxygruppe der nachstehenden Formel (II):



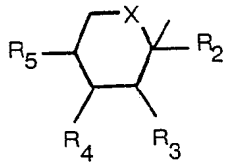
(II)

ausbilden können, worin

R_6 und R_7 gleich oder verschieden sind und Wasserstoff oder Neideralkyl bedeuten oder Alkyl darstellen und unter Ausbildung eines Cyclopentyl- oder Cyclohexylringes verbunden sind.

13. Verfahren zur Herstellung eines Sulfamats nach Anspruch 1, umfassend

(a) Umsetzen eines Alkohols der Formel RCH_2OH mit einem Chlorsulfamat der Formel $ClSO_2NHR_1$ in Gegenwart eines Base, wobei R einen Rest der Formel (III)



(III)

darstellt und wobei X, R_1, R_2, R_3, R_4 und R_5 wie in Anspruch 1 definiert sind, oder

(b) Umsetzen eines Alkohols der Formel RCH_2OH mit Sulfurylchlorid in Gegenwart einer Base zur Ausbildung eines Chlorsulfats der Formel RCH_2OSO_2Cl, worin R wie vorstehend definiert ist, und

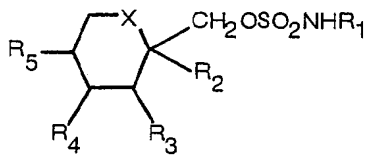
(i) falls R_1 in der Formel (I) Wasserstoff oder Alkyl bedeutet, Umsetzen dieses Chlorsulfats mit einem Amin der Formel R_1NH_2, oder

(ii) falls R_1 in Formel (I) Wasserstoff bedeutet, Umsetzen dieses Chlorsulfats mit einem Metallazid der Formel $RCH_2OSO_2N_3$ und Reduzieren dieses Azidosulfats.

14. Verfahren zur Herstellung einer pharmazeutische Zusammensetzung, umfassend ein Vermischen eines Sulfamats nach Anspruch 1 mit einem pharmazeutisch annehmbaren Träger.

Revendications

1. Sulfamate répondant à la formule (I) suivants:



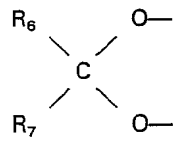
(I)

dans laquelle

X est CH_2 ou un atome d'oxygène;

R_1 est un atome d'hydrogène ou un groupe alkyle; et

R_2, R_3, R_4 et R_5 sont indépendamment un atome d'hydrogène ou un groupe alkyle inférieur et, lorsque X est CH_2, R_4 et R_5 peuvent se réunir pour former un cycle benzénique et, lorsque X est un atome d'oxygène, R_2 et R_3 et/ou R_4 et R_5 peuvent être ensemble un groupe méthylènedioxy répondant à la formule (II) suivante:



(II)

dans laquelle

R_6 et R_7 sont identiques ou différents et son un atome d'hydrogène, un groupe alkyle inférieur ou sont un groupe alkyle et se réunissent pour former un cycle cyclopentyle ou cyclohexyle.

2. Sulfamate selon la revendication 1, dans lequel

X est un atome d'oxygène; et

R_2 et R_3 et R_4 et R_5 sont ensemble des groupes méthylènedioxy répondant à la formule (II).

3. Sulfamate de la revendication 1, dans lequel

X est est CH_2; et

R_4 et R_5 se réunissent pour former un cycle benzénique.

4. Sulfamate selon la revendication 3, dans lequel R_2 et R_3 sont un atome d'hydrogène.

5. Sulfamate selon la revendication 1, dans lequel ce groupe alkyle représente par R_1 est un groupe alkyle en C_1 à C_4; ce groupe alkyle inférieur représenté par R_2, R_3, R_4 et R_5 ests un groupe alkyle en C_1 à C_3; et ce groupe alkyle inférieur représenté par R_6 et R_7 est un groupe alkyle en C_1 à C_3.

6. Sulfamate selon la revendication 1, dans lequel ce sulfamate répondant à la formule (I) est choisi dans le groupe constitué de:

tétrahydro-2H-pyran-2-yl)méthane sulfamate;

(1-méthylcyclohexyl)méthane sulfamate;

2,3:4,5-bis-O-(1-méthyléthylidène)-ß-D-fructopyranose sulfamate;

2,3:4,5-bis-O-(1-méthyléthylidène)-ß-D-fructopyranose méthylsulfamate; ou

ester de l'acide (1,2,3,4-tétrahydro-2-naphtalényl)méthyl sulfamique.

7. Sulfamate selon la revendication 6, dans lequel ce sulfamate est le 2,3:4,5-bis-O-(1-méthyléthylidène)-ß-D-fructopyranose sulfamate.

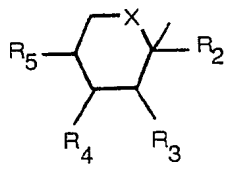
8. Sulfamate selon la revendication 6, dans lequel ce sulfamate est l'ester de l'acide (1,2,3,4-tétrahydro-2-naphtalényl)méthyl sulfamique.

9. Composition pharmaceutique comprenant un sulfamate selon l'une quelconque des revendications précédentes et un excipient pharmaceutique acceptable.

10. Composition pharmaceutique selon la revendication 9, dans lequel ce sulfamate est présent à une dose unitaire de 10 à 500 mg du sulfamate.

11. Sulfamate selon l'une quelconque des revendications 1 à 8, ou composition pharmaceutique selon la revendication 9 ou 10, pour l'utilisation le traitement des convulsions chez les mammifères.

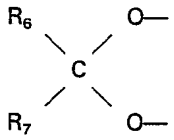
12. Chlorosulfate répondant à la formule RCH_2OSO_2Cl ou azodisulfate répondant à la formula $RCH_2OSO_2N_3$ dans laquelle R répond à la formule (III) suivante:



(III)

dans laquelle

R_2, R_3, R_4 et R_5 sont indépendamment un atome d'hydrogène ou un groupe alkyle inférieur et, lorsque X est CH_2R_4 et R_5 peuvent être des groupes alcène réunis pour former un cycle benzénique et, lorsque X est un atome d'oxygène, R_2 et R_3 et/ou R_4 et R_5 peuvent former ensemble un groupe méthylènedioxy répondant à la formule (II) suivante:



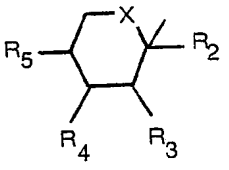
(II)

dans laquelle

R_6 et R_7 sont identiques ou différents et sont un atome d'hydrogène, un groupe alkyle inférieur ou sont un groupe alkyle et se réunissent poure former un cycle cyclopentyle ou cyclohexyle.

13. Procédé de préparation d'un sulfamate selon la revendication 1, comprenant

(a) la réaction d'un alcool répondant à la formule RCH_2OH avec un chlorosulfamate répondant à la formule $XISO_2NHR_1$ en présence d'une base, dans laquelle R est une partie répondant à la formule (III):



(III)

et dans laquelle X, R_1, R_2, R_3, R_4 et R_5 sont tels que définis dans la revendication 1, ou

(b) la réaction d'un alcool répondant à la formule RCH_2OH avec le chlorure de sulfuryle en présence d'une base, pour produire un chlorosulfate répondant à la formule RCH_2OSO_2Cl, dans laquelle R est tel que défini ci-dessus, et

(i) lorsque R_1, dans la formule (I), est un atome d'hydrogène ou un groupe alkyle, la réaction de ce chlorosulfate avec une amine répondant à la formule $R_1 NH_2$ ou

(ii) lorsque R_1, dans la formule (I), est un atome d'hydrogène, la réaction de ce chlorosulfate avec un azide métallique répondant à la formule $RCH_2OSO_2N_3$ et la réduction de cet azidosulfate.

14. Procédé de préparation d'une composition pharmaceutique comprenant la mélange d'un sulfamate selon la revendication 1 avec un excipient pharmaceutiquement acceptable.